ADAPTATION TO INTERMITTENT HYPOXIA: DYNAMICS OF BLOOD OXYGEN SATURATION AND SOME HEMATOLOGICAL PARAMETERS

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Adaptation to hypoxia is an important object of medical research. The aim of this study was to investigate the dynamics of blood oxygen saturation (SpO_2), arterial blood pressure (BP), red blood cells, reticulocytes, hemoglobin and erythropoietin (EPO) concentrations during intermittent hypoxic training (IHT). The study was conducted in 11 healthy male volunteers; 2 regimens were tested: 11 and 14 days of IHT at F_IO_2 = 9%. Exposure to the hypoxic gas mixture caused a reduction in SpO_2 by an average of 20.4% ($p < 0.05$), a 22% increase in the heart rate ($p < 0.05$) and a 4.5% decrease in diastolic BP ($p < 0.05$) relative to the initial levels. After 11 days of IHT training, the reticulocyte count was increased by 16.6% ($p < 0.05$), and there was a distinct tendency to elevated red blood cells ($p > 0.05$) and hemoglobin ($p > 0.05$). EPO concentrations declined by 44.2% ($p < 0.05$) relative to the initial level. Extending the regimen to 14 days resulted in a 3.9% increase in red blood cell count ($p < 0.05$) and a 4.7% elevation of hemoglobin concentrations ($p < 0.05$), accompanied by the recovery of the initial reticulocyte count. The applied 2-week IHT regimen resulted in the increased red blood cell count and elevated hemoglobin, suggesting an improvement in the oxygen-carrying capacity of the blood. The proposed regimen can be used to improve physical performance of individuals working in extreme environmental conditions.

Keywords: intermittent hypoxic training, blood oxygen saturation, erythropoietin, hemoglobin, red blood cells, reticulocytes, arterial blood pressure.

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АДАПТАЦИЯ К ИНТЕРВАЛЬНОЙ ГИПОКСИИ: ДИНАМИКА НАСЫЩЕНИЯ КРОВИ КИСЛОРОДОМ И НЕКОТОРЫХ ГЕМАТОЛОГИЧЕСКИХ ПОКАЗАТЕЛЕЙ

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Адаптация к гипоксии является одной из актуальных проблем медицины. Целью работы было изучить динамику насыщения крови кислородом (SpO_2), артериального давления (АД), показателей красного ростка крови и уровня эритропоэтина (Эпо) в процессе интервальных гипоксических тренировок (ИГТ). При участии 11 мужчин-добровольцев проведено две серии исследований с 11- и 14-суточным курсом ИГТ при F_IO_2 = 9%. Дыхание воздухом с пониженным PO_2 приводило к уменьшению SpO_2 в среднем на 20,4% ($p < 0,05$), увеличению частоты сердечных сокращений на 22% ($p < 0,05$) и снижению диастолического АД на 4,5% ($p < 0,05$) по отношению к исходным значениям. После 11-суточного курса ИГТ наблюдали увеличение в крови числа ретикулоцитов на 16,6% ($p < 0,05$), тенденцию к увеличению числа эритроцитов ($p > 0,05$) и содержания гемоглобина ($p > 0,05$). Уровень Эпо по сравнению с исходной величиной снижался на 44,2% ($p < 0,05$). Увеличение курса ИГТ до 14 суток привело к повышению числа эритроцитов на 3,9% ($p < 0,05$) и содержания гемоглобина на 4,7% ($p < 0,05$), что сопровождалось уменьшением числа ретикулоцитов до исходного уровня. Двухнедельный курс ИГТ приводит к увеличению в крови числа эритроцитов и содержания гемоглобина, что указывает на повышение кислородной емкости крови. Разработанный протокол ИГТ может быть использован при подготовке специального контингента лиц к работам с повышенной физической нагрузкой в экстремальных условиях окружающей среды.

Ключевые слова: интервальные гипоксические тренировки, насыщение крови кислородом, эритропоэтин, гемоглобин, эритроциты, ретикулоциты, артериальное давление.

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Exploring the impact of the reduced partial pressure of oxygen (PO_2), i.e. hypoxic hypoxia, on the human body is an important area of medical research. Depending on the degree of environmental PO_2 reduction, hypoxia can either provoke pathology or exert a revitalizing effect [1–10]. The studies by Felix Z. Meerson generated a vast array of data suggesting that

adaptive hypoxic training could improve overall endurance and tolerance of hypoxia or other harsh environmental conditions, including extreme cold and physical strain; Meerson's works provided a rationale for his concept of cross adaptation, the general mechanism of adaptation and prophylaxis [11, 12].

Success in decoding the molecular mechanism of oxygen homeostasis has become one of the major advances in biology made in the last 3 decades. The key regulators of oxygen homeostasis are hypoxia-inducible factors (HIFs) [13], of which HIF-1 is highly crucial and well-studied. HIF-1 is a heterodimer composed of an oxygen-dependent subunit HIF-1α and a structural subunit HIF-1β. The concentration and stability of HIF-1α and its transcriptional activity are directly dependent on PO_2 in the cell [14, 15]. Under reduced PO_2, HIF-1α initiates a cascade of gene-mediated cellular and systemic reactions conducive to delivering enough oxygen to tissues and subsequent oxygen uptake. HIF-1 and HIF-2 stimulate production of erythropoietin (EPO) by the kidneys. EPO is a hormone that regulates production of red blood cells in the bone marrow [16]; in turn, red blood cells carry oxygen from the lungs to other tissues.

This theoretical thesis is in good agreement with the experimental data demonstrating that long exposure to an altitude > 2,200 m leads to an increase in serum EPO concentrations [17] and altitude acclimatization is characterized by polycythemia, elevated hemoglobin and increased oxygen-carrying capacity of the blood [1, 3, 18–20]. However, the associations between EPO levels, hematological parameters of red blood cells and physiological effects of hypoxia may not always be very pronounced in intermittent hypoxic training (IHT), which is used to stimulate adaptation to hypoxia. For example, no increase in EPO concentrations, hematological parameters of red blood cells or improved endurance performance were observed in distance runners undergoing a 4-week normobaric IHT program (5 min of normoxia followed by 5 min of hypoxia, 70 min per session, 5 times a week; F_IO_2 = 12% at week 1, F_IO_2 = 11% at week 2, F_IO_2 = 10% at weeks 3 and 4) [21]. Another study conducted in athletes found no significant differences in the hematological parameters of red blood cells and hemoglobin mass at baseline and after 4 weeks of IHT in a hypobaric chamber (3 h a day, 5 days a week, pressure equivalent to that at 4,000–5,500 m), although there was a twofold increase in EPO concentrations after exposure to the hypoxic environment [22]. Another study reported complement activation, increased phagocytic activity of neutrophils and elevated immunoglobulins in 10 healthy male volunteers undergoing a 2-week normobaric IHT program (5 min of hypoxia followed by 5 min of normoxia, 4 times a day [23]. However, the positive effects of IHT observed in the cited study were not accompanied by EPO elevation, increased erythrocyte count or heightened hemoglobin concentrations. One more publication reported the absence of changes in hematocrit and hemoglobin concentrations in 9 healthy males undergoing a 12-day normobaric IHT program (2h a day at F_IO_2 ~13%) [24]; however, by day 5 their reticulocyte count was elevated.

Considering that IHT is widely used in clinical, sports, aviation and space medicine [7, 8, 25–27], it is important to study its effects on the human body, the underlying mechanisms, the efficacy of different IHT regimens and approaches to their optimization [28]. The aim of this study was to investigate changes in oxygen saturation, arterial blood pressure, hematological parameters of red blood cells and EPO concentrations throughout a 2-week IHT program.

METHODS

The study was carried out on 11 apparently healthy male volunteers aged 21–32 years (the mean age was 25.3 ± 1.5 years; the mean weight, 81.5 ± 3.3 kg; the mean height, 180.4 ± 2.2 cm). The following inclusion criteria were applied: approval by the medical board and voluntary consent to participate.

IHT sessions were conducted using a Bio-Nova-204 system for hypoxic therapy (Bio-Nova; Russia) that allows delivering a hypoxic gas mixture to 2 patients at a time. During the sessions, the participants remained seated. The mixture was delivered through a mask pressed tightly against the face, in a well-ventilated room for physiological tests involving humans. The sessions were administered on a daily basis; each session lasted 60 min and consisted of 6 cycles of breathing the hypoxic gas mixture (5 min) followed by breathing ambient air (5 min). Thus, each session included six 5-minute long periods of inhaling the hypoxic has mixture, and the total duration of hypoxic exposure was 30 min. During the first IHT session, F_IO_2 was 10%, which corresponds to P_IO_2 ~76 mmHg. During the second and the remainder sessions, F_IO_2 was 9% (P_IO_2 ~68.5 mmHg). In the first part of the experiment, an 11-day regimen was applied to 5 participants; in the second part, the regimen was extended to 14 days and was administered to 6 participants.

During the sessions, the physiological and subjective responses of the participants to the inspired low-oxygen mixture were closely monitored. Systolic (SBP) and diastolic (DBP) blood pressures, SpO_2 and heart rate (HR) were measured at baseline and during the inhalation of the hypoxic mixture using a PVM-2703 monitor (Nihon Kohden Corporation; Japan).

For blood tests, fasting blood samples were drawn from a basilic vein in the morning prior to commencing the program and upon completion of the first (11 days) and second (14 days) parts of the experiment. Measurements were done using an automated hematology analyzer XN-3000 (Sysmex Corporation; Japan). EPO was measured using an Immulite 2000 XPi analyzer (Siemens; Germany) before starting the 11-day regimen and upon its completion.

Prior to and after completing the extended 14-day IHT regimen, a functional test previously described in [29] was

Table 1. Oxygen saturation (SpO_2), heart rate (HR), systolic (SBP) and diastolic (DBP) pressures in the participants during hypoxic gas breathing

Stage of the experiment	SpO_2, %	HR, min^{-1}	SBP mmHg	DBP, mmHg
Before IHT	97.0 ± 0.5	71.7 ± 4.0	127.6 ± 3.1	80.2 ± 1 .8
IHT № 1	75.3 ± 1.3*	89.0 ± 4.3*	125.3 ± 6.1	77.8 ± 1.3
IHT № 4	76.5 ± 3.2*	90.6 ± 1.3*	124.7 ± 7.3	80.7 ± 5.4
IHT № 8	78.6 ± 2.3*	85.3 ± 4.7*	127.5 ± 7.0	76.7 ± 2.6
IHT № 11	78.1 ± 1.9*	84.6 ± 5.5*	123.4 ± 4.8	73.7 ± 1.8*
IHT № 14	77.6 ± 2.6*	86.8 ± 4.1*	127.8 ± 4.8	74.2 ± 2.8*

Note: IHT — intermittent hypoxic training; * — $p < 0.05$ for comparisons with pretraining data

Table 2. Hematological parameters of red blood cells and erythropoietin levels before and after the IHT program

Parameter	11-day IHT regimen		14-day IHT regimen	
	Before IHT	After IHT	Before IHT	After IHT
Red blood cell count, $\times10^{12}$/L	4.85 ± 0.38	5.0 ± 0.32	5.1 ± 0.17	5.3 ± 0.23*
Hemoglobin, g/L	138.2 ± 5.38	143.8 ± 7.91	150.2 ± 4.2	157.3 ± 5.73*
Erythropoietin, mME/ml	7.35 ± 2.5	4.1 ± 0.96*	–	–
Hematocrit, %	42.4 ± 2.4	43.3 ± 2.6	45.4 ± 1.13	46.4 ± 1.83
Reticulocyte count, $\times10^{9}$/L	71.7 ± 4.2	83.6 ± 6.7*	73.9 ± 5.2	68.9 ± 3.5

Note: * — $p < 0.05$ for comparisons with pretraining data.

performed to assess adaptation to intermittent hypoxia. The test determined the time it took SpO_2 to decline from the initial level to 80% during hypoxic gas breathing, with F_IO_2 =10% (Td SpO_2), and the time it took SpO_2 to recover from 80% to the initial level after the participants stopped inhaling the hypoxic gas (Tr SpO_2).

Statistical analysis was carried out in Mircosoft Excel 2016 (16.0.5071.1000) (Microsoft Corporation; USA). Normality of data distribution was tested using the Kolmogorov–Smirnov test. Significance of differences was assessed using Student's *t* test and the nonparametric Wilcoxon *T* test. Differences were considered significant at $p < 0.05$. The results are presented in the tables below as M ± *m*.

RESULTS

Mean SpO_2, HR, SBP and DBP measured during hypoxic gas breathing are provided in Table 1. Following exposure to the hypoxic gas mixture, SpO_2 decreased significantly by an average of 20.4% ($p < 0.05$), HR increased by 22% ($p < 0.05$) and DBP lowered by 4.5% ($p < 0.05$) relative to the initial levels. DBP did not change significantly. Subjectively, the participants tolerated the applied IHT protocol well and did not complain of any discomfort. SpO_2, HR and blood pressure went back to normal when the participants were breathing ambient air. The same dynamics repeated themselves over the next cycles throughout the session.

Table 2 shows changes in the hematological parameters of red blood cells and EPO during IHT. We observed a significant increase in the absolute reticulocyte count (16.6%; $p < 0.05$) following the completion of the 11-day IHT regimen. There was a distinct tendency toward elevated red blood cells and total hemoglobin ($p > 0.05$) in the setting of the increased reticulocyte count. At the same time, serum EPO concentrations declined by 44.2% ($p < 0.05$) relative to the initial values. In the second part of the experiment, the duration of IHT was extended to 14 days, which led to a significant 3.9% increase in red blood cells ($p < 0.05$) and a 4.7% increase in hemoglobin concentrations ($p < 0.05$) relative to the pretraining values. However, in contrast to the 11-day regimen, the absolute reticulocyte count was not elevated after 14 days of IHT. Moreover, the absolute reticulocyte count did not differ significantly from the initial level and was by 6.7% lower than at baseline ($p > 0.05$). On average, hematocrit concentrations were slightly above baseline values in both parts of the experiment. However, the changes were insignificant ($p > 0.05$).

Fig. 1 features the results of the functional test during hypoxic gas breathing (F_IO_2 =10%). After 14 days of IHT, the test showed a significant increase (by 93. 5%) in the time it took SpO_2 to lower to 80% ($p < 0.05$) and a statistically significant reduction by 44% ($p < 0.05$) in SpO_2 recovery time relative to the pretraining values. Considering the detected shifts in the hematological parameters of red blood cells, we hypothesize that these changes might be associated with the increased oxygen-carrying capacity of the blood following the IHT program and the developed adaptation in response to intermittent exposure to hypoxic hypoxia.

DISCUSSION

Normally, normobaric and hypobaric IHT regimens rely on P_IO_2 varying between 114 and 76 mmHg [7, 25, 26, 30–34]. In our study, P_IO_2 was maintained at 76 mmHg during the first training session but then adjusted to 68.5 mmHg for the remainder sessions. During the 14-day regimen, the participants did not have any health complaints or report discomfort. HR and blood pressure were within the normal reference range, suggesting that healthy men could tolerate the applied protocol well.

Table 1 demonstrates that the most pronounced changes in SpO_2 and HR were observed in the first part of week 1 of training. Starting from week 2, the decrease in SpO_2 became less pronounced, HR was growing more slowly, and DBP was significantly decreased. According to the literature, these changes might be associated with a relatively increased activity of the parasympathetic nervous system during adaptation to intermittent hypoxia [7, 8, 35] and with improved tolerance to hypoxia [36].

Our experiment demonstrates that changes in the hematological parameters of red blood cells become noticeable and statistically significant after 1.5 weeks of training. They encompass increased production of reticulocytes in the bone marrow and their mass release into the bloodstream. Today it is believed that elevated reticulocytes in the blood reflect the increased production of EPO, the major erythropoiesis regulator [37]. Under reduced P_IO_2, serum EPO concentrations peak in 24–48 h and can decline then a week later, approximating the initial level [38]. Erythropoiesis is a slowly activated process. Reticulocytosis becomes noticeable as late as 3–4 days after EPO elevation [37]. Our findings are consistent with the results of other studies investigating EPO dynamics. Low EPO levels and increased reticulocyte count detected after the completion of the 11-day regimen are in good agreement with the absence of reticulosis, significantly elevated red blood cells and increased hemoglobin after 14 days of IHT.

Apart from being the main physiological erythropoiesis regulator, EPO is involved in regulating the functions of the brain stem structures that control the respiratory system; specifically, EPO participates in the regulation of the hypoxic ventilatory response [39, 40]. A study measured the levels of EPO mRNA in the brain stem of rats following 2 weeks of intermittent hypoxic exposure at F_IO_2 equaling 12% or 7% [41]. The study found that EPO mRNA tended to decline following 2 weeks of moderately intense exposure to hypoxia (12% O_2) and dropped more than twofold after a more intense hypoxia regimen (7% O_2). The researchers linked the reduced EPO production to the completion of some adaptation stage after

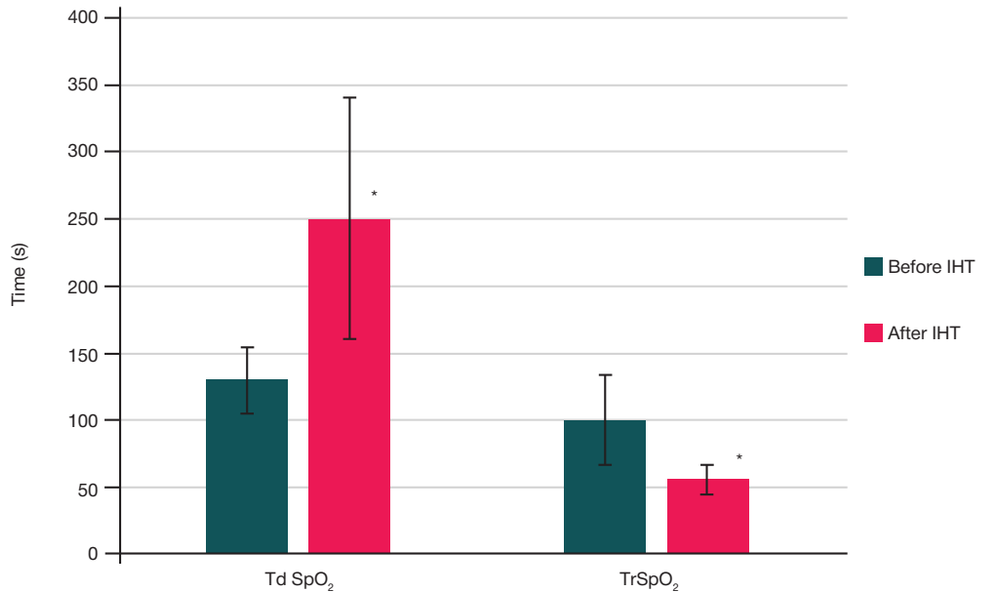

Fig. 1. $TdSpO_2$ and $TrSpO_2$ values during hypoxic gas beathing (F_iO_2 = 10%) before and after the 14-day IHT regimen. * — $p < 0.05$ for comparisons with pretraining values

IHT. However, it should be born in mind that EPO expression and the intensity of erythropoiesis are interrelated through O_2-dependent processes. There are reasons to assume that the initial elevation of serum EPO occurs when EPO production exceeds its utilization in the bone marrow, whereas EPO levels start to decline when increased erythropoiesis leads to the increased utilization of EPO in the bone marrow [42]. Thus, at each stage of adaptation to intermittent hypoxia a dynamic equilibrium will be maintained between the required level of EPO production in the kidneys and its utilization in the bone marrow.

The term “hypoxic dose” is often used in the academic literature about the hematological effects of hypobaric and normobaric IHT. It characterizes the capacity of an IHT protocol to have a sufficient stimulating effect on erythropoiesis by activating EPO production [26, 43]. This characteristic is determined by the PO_2 in the inspired air, the duration of hypoxic exposure in each cycle, periodicity of alternating exposures to inspired ambient and hypoxic air, the frequency of training sessions per week, and the total duration of the IHT program. We found that the applied 2-week regimen, which included 1-hour long daily sessions at PO_2 ~ 68.5 mmHg, was enough to activate erythropoiesis, increase red blood cell count, hemoglobin and oxygen-carrying capacity of the blood. With a relatively brief total exposure to a hypoxic environment, the applied hypoxic dose might not be sufficient to increase the total hemoglobin mass [32, 44].

In sports medicine, IHT has long been used to prepare athletes for competitions and improve oxygen uptake and physical performance [45]. However, in IHT the increased oxygen-carrying capacity of the blood is not the only contributor to better endurance performance [46]. Activated under reduced PO_2, HIF-1 was initially described as a transcription regulator for the EPO gene [47]. Later it was discovered that HIF-1 can activate a staggering variety of genes whose involvement is not limited to adaptive hematological responses [40]. HIF-1 plays a crucial role in the response of the cardiovascular and respiratory systems to hypoxia [48]. It initiates complex responses aimed at improving lung ventilation, angiogenesis, maintaining pH and acid-base metabolism in muscle tissue [46], improving oxygen uptake by cells [28]. Each of the listed non-hematological IHT effects can contribute to improving physical performance independent of the increased oxygen-carrying capacity of the blood.

CONCLUSION

The proposed regimen included 1-hour long normobaric IHT sessions at PO_2 ~ 68.5 mmHg and was administered to a group of healthy male volunteers. The regimen simple and well tolerated by the participants; it provoked moderate transitory changes in cardiorespiratory parameters. The 2-week IHT program based on the proposed regimen resulted in the increased red blood cell count and elevated hemoglobin, suggesting an improvement in the oxygen-carrying capacity of the blood. The proposed regimen can be used to improve physical performance of individuals working in extreme environmental conditions.

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